

# Recent Advances in Preoperative Hyperthermochemoradiotherapy for Patients With Esophageal Cancer

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**Background and Objectives:** Hyperthermochemoradiotherapy (HCR) has been performed on numerous patients with esophageal cancer. The purpose of this study is to demonstrate the recent advances in HCR.

**Methods:** From 1965 to 1997, 294 patients given preoperative chemoradiotherapy (CR) or HCR were classified according to the anticancer agent that was administered (CR; group A given bleomycin (BLM); group B given cis-diamminedichloroplatinum (II) (CDDP), HCR; group C given BLM; and Group D given CDDP). The local response and the long-term results were investigated.

**Results:** The cases in which CR or HCR was evaluated to be effective numbered 44 (48.4%) in group A, 22 (73.3%) in group B, 79 (63.7%) in group C, and 36 (73.5%) in group D. A significant difference was observed between groups A and B ( $P < 0.05$ ). The highest incidence of markedly effective cases was observed in group D. The 5-year survival rates for the group A and B patients were 17.2% and 43.9%, respectively ( $P < 0.01$ ), while the same rates for those of groups C and D were 25.6% and 57.8%, respectively ( $P < 0.05$ ). Our results thus showed CDDP to have a greater effect than BLM, while HCR had a greater effect than CR.

**Conclusions:** Preoperative HCR has improved thanks to recent advances in anticancer agents. *J. Surg. Oncol.* 1998;69:224–229. © 1998 Wiley-Liss, Inc.

**KEY WORDS:** hyperthermia; anticancer agent; esophageal cancer; preoperative therapy

## INTRODUCTION

Owing to recent improvements in diagnostic techniques, the incidence of early esophageal cancers has been increasing [1–3]. However, since the majority of patients with esophageal cancer tend to have widespread disease at the time of detection, esophageal cancer still remains one of the most difficult neoplasms to be controlled by surgery alone [4]. As a result, both radiotherapy and chemotherapy have been applied to the patients with advanced esophageal cancer at many institutes in order to obtain either a preoperative downstaging of the primary tumor or to control the disease conservatively [5–11].

At many institutes, various basic studies concerning hyperthermia have been performed, and this treatment

has been proved to be intensely cytotoxic, especially to malignant cells when combined with either anticancer agents or irradiation in studies both in vitro [12–21] and in vivo [22–28]. Based on the results of these experiments, we applied hyperthermochemoradiotherapy (HCR) using a radiofrequency system with an endotracheal electrode [29] mainly to clinical patients with advanced esophageal cancer preoperatively. We also previously reported the long-term effects of preoperative HCR on survival in instances of cancer of the esophagus [30–34].

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Bleomycin (BLM) was shown to be effective against squamous cell carcinoma and its effect was augmented by hyperthermia [16,25–27]. The combined administration of hyperthermia, BLM, and irradiation at doses that were individually nontoxic was reported to lead to significant antitumor effects [12]. In our department, BLM had been mainly applied to preoperative HCR up until the 1980s. However, the risk of pulmonary fibrosis, a major side effect of BLM, has limited the dosage of BLM given to patients, which thus resulted in an unsatisfactory prognosis in the cases receiving preoperative radiation with BLM. Therefore, other agents that are more effective against squamous cell carcinoma and less toxic to humans have been called for. Cis-diamminedichloroplatinum (II) (CDDP), is an antineoplastic drug commonly used against a wide spectrum of human malignancies, and its cytotoxicity has been reported to be enhanced by hyperthermia both in vitro [17–19] and in vivo [27,28]. Based on the results of these experiments, we have applied CDDP to HCR as a key drug for patients with esophageal cancer since 1990 instead of BLM. 5-Fluorouracil (5-FU) is another drug with a definite positive effect for the treatment of solid tumors and there have also been some reports on the combined effect of 5-FU plus hyperthermia [20,21]. Many recent trials of neoadjuvant therapy for patients with esophageal cancer showed that the combination of CDDP/5-FU with or without radiotherapy was considered to be the standard protocol of treatment for the patients with esophageal cancer [35–38]. Our preoperative HCR regimen has also changed along with the advances of these basic and clinical studies for anticancer agents.

We herein report the clinical results of preoperative chemoradiotherapy (CR) without hyperthermia or HCR for patients with esophageal cancer, while particularly focusing on the changes in the regimens of these therapies. The regimens using CDDP were compared with the regimens using BLM with respect to both CR and HCR in a retrospective fashion. Furthermore, the effectiveness of HCR in the regimen using CDDP was also investigated in comparison with that of CR plus CDDP.

## MATERIALS AND METHODS

### Patients

From February 1965 to March 1997, at the Department of Surgery II, Kyushu University, 736 cases of esophageal cancer were surgically treated. Among these, 121 and 173 were given either preoperative CR (CR group) or HCR (HCR group), respectively. These 294 patients given preoperative CR or HCR were classified into the following four groups according to the treatment regimens. The CR group was classified into the following two groups; group A who received regimen A (Fig. 1) using BLM as the chemotherapeutic drug in the early period (1965–1990) and group B who received regimen

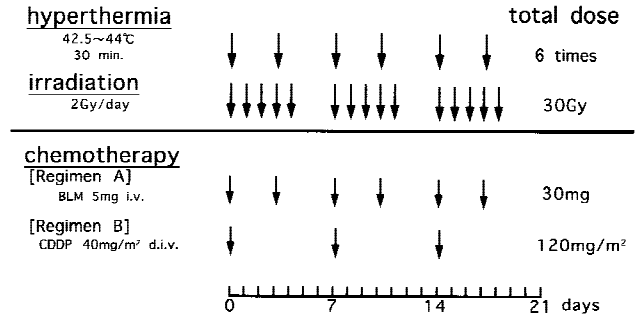


Fig. 1. The hyperthermochemoradiotherapy regimen for patients with esophageal cancer.

B (Fig. 1) using CDDP as the chemotherapeutic drug in the recent period (1990–1997). The HCR group was also divided into the following two groups; group C who received regimen A in the early period and group D who received regimen B in the recent period.

We evaluated the histopathological effects and the long-term survival rates among these groups. In these comparisons, no significant differences were observed with regard to such background factors as age, sex, depth of invasion, lymph node metastasis, and TNM stage (Table I).

### Technique of Hyperthermia and Treatment Schedule

Esophageal hyperthermia was clinically applied using a radiofrequency system with an endotract electrode (Endoradiotherm 100A, Endoradiotherm 200A, Olympus, Tokyo, Japan) [29]. A long, thin electrode was placed in the esophagus and a broad, wide counter electrode was fixed to the chest surface, which made the localization of the electromagnetic field feasible in the esophagus. The temperature was monitored by the endotract electrode, thus indicating the tumor surface to be controlled by a cooling water system within the silicon balloon, which eliminates the gap between transmitter and lesion. Thermosensors attached to the balloon surface indicated the temperature of the tumor surface.

Figure 1 shows the CR or HCR regimens in each period. The HCR regimen consisted of irradiation given 5 days per week, and two fractions of hyperthermia per week, combined with intravenous chemotherapy. Hyperthermia and chemotherapy were simultaneously given 1 hr after radiotherapy with a 6-mV X-ray using the opposed A-P portal technique. The HCR was scheduled for 3 weeks preoperatively with a total of 30 Gy of irradiation, chemotherapy, and six exposures of hyperthermia. The patients who received preoperative CR without hyperthermia were given the same regimen as HCR except for the hyperthermia.

From 1965 to 1990, 5 mg of BLM was administered six times simultaneously with hyperthermia for a total of

**TABLE I. Clinicopathological Features of Patients in the CR or HCR Groups\***

	CR group (n = 121)		HCR group (n = 173)	
	Group A (n = 91) (%)	Group B (n = 30) (%)	Group C (n = 124) (%)	Group D (n = 49) (%)
Age (years)	63.2 ± 7.3	64.2 ± 9.7	62.4 ± 10.1	62.5 ± 7.8
Sex (M:F)	74:17	26:4	107:17	43:6
Microscopic invasion to adventitia				
Negative	13 (14.3)	9 (30.0)	40 (32.3)	22 (44.9)
Positive	78 (85.7)	21 (70.0)	84 (67.7)	27 (55.1)
Microscopic lymph node metastasis				
Negative	49 (53.8)	17 (56.7)	65 (52.4)	27 (55.1)
Positive	42 (46.2)	13 (43.3)	59 (47.6)	22 (44.9)
Pathological TNM				
I, II	36 (39.6)	13 (43.3)	60 (48.4)	30 (61.2)
III, IV	55 (60.4)	17 (56.7)	64 (51.6)	19 (38.8)

\*Values are not significant. (group A vs. B, group C vs. D, group B vs. D). Values in parentheses are percentages.

**TABLE II. Histopathological Evaluation of the Local Effects of Each Period in the CR Group and HCR Group\***

	Group A (n = 91) (%)	Group B (n = 30) (%)	<i>P</i> value
CR group (n = 121)			
Grade 0, 1	47 (51.6)	8 (26.7)	<i>P</i> < 0.05
Grade 2	35 (38.5)	19 (63.3)	
Grade 3	9 (9.9)	3 (10.0)	<i>P</i> = 0.045
	Group C (n = 124) (%)	Group D (n = 49) (%)	<i>P</i> value
HCR group (n = 173)			
Grade 0, 1	45 (36.3)	13 (26.5)	<i>P</i> = 0.053
Grade 2	57 (46.0)	19 (38.8)	
Grade 3	22 (17.7)	17 (34.7)	

\*A significant difference was observed between group B and group D (*P* < 0.05).

30 mg (regimen A). From 1990 to 1997, 40 mg/m<sup>2</sup> of CDDP was administered three times during the treatment period for a total of 120 mg/m<sup>2</sup> (regimen B). All operations were performed from 7 to 14 days after terminating the preoperative therapy in each regimen.

### Microscopic Evaluation

Detailed histological evaluations were made on the resected specimens, and the effect of preoperative therapy was then microscopically classified into three grades divided by the guidelines for pathological studies on cancer of the esophagus established by the Japanese Society for Esophageal Diseases [39]. The details are as follows. Markedly effective (grade 3) denotes that all cancer cells were destroyed with no evidence of viable

cancer cells; moderately effective (grade 2), most (more than two-thirds) of the cancer cells were damaged, despite the continued presence of viable cancer cells; in this study, slightly effective cases (grade 1) and ineffective cases (grade 0) were regarded as ineffective. The TNM stage was determined based on the histological evaluations and the staging was determined based not only on the viable cancer tissue but also on the cancer scar tissue.

### Statistical Analysis

Results were analyzed by the chi-square and Student *t*-tests. The survival curves were estimated using the Kaplan-Meier procedures and comparisons were analyzed by the generalized Wilcoxon test. A *P* value of less than 0.05 was considered statistically significant.

## RESULTS

### Histopathological Effectiveness of Preoperative Treatment

According to the histopathological examination of the resected specimens of the CR group, 9 (9.9%) and 35 (38.5%) patients showed a marked and moderate response in group A, respectively, and 3 (10.0%) and 19 (63.3%) showed a marked and moderate response in group B, respectively. These rates demonstrated a significant difference between the groups (*P* < 0.05). According to the same comparison of the HCR group, 22 (17.7%) and 57 (46.0%) patients showed a marked and moderate response in group C, respectively, and 17 (34.7%) and 19 (38.8%) in Group D, respectively (*P* = 0.053). Based on these findings, the regimen using CDDP clearly caused a significantly increased anticancer effects in the patients with esophageal cancer. A significant difference in the histopathological effect between

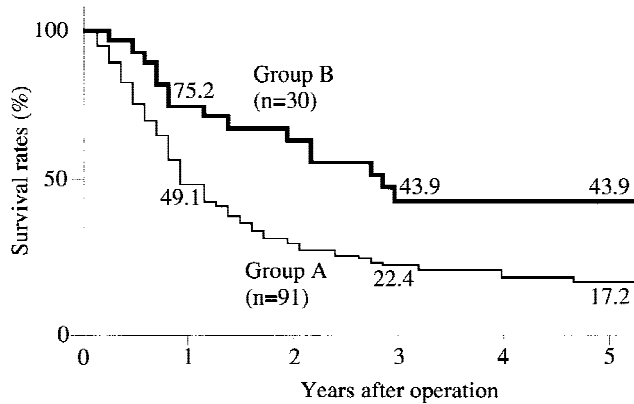


Fig. 2. The survival curves of the patients undergoing esophagectomy after CR according to treatment. Statistically significant value,  $P = 0.006$ .

groups B and D was also observed ( $P < 0.05$ ). The combination of hyperthermia with irradiation and chemotherapy thus had a significantly greater anticancer effect in patients with esophageal cancer than did the combination of irradiation with chemotherapy without hyperthermia (Table II).

#### Long-Term Effectiveness of Preoperative Therapy

Figure 2 shows the survival curves of the patients who were treated surgically after preoperative CR. Since we usually perform an esophagectomy without any preoperative treatment in the cases of early stage cancer, most cases consisted of advanced disease in this study. The 3-year and 5-year survival rates for the group A patients were 22.4% and 17.2%, respectively, whereas those in group B were 43.9% and 43.9%, respectively. The prognosis for the group B patients was also significantly better than that for group A ( $P < 0.01$ ).

In the cases treated surgically after preoperative HCR, the survival rates for group D patients were significantly higher than those for group C ( $P < 0.05$ ). The 3-year and 5-year survival rates for the patients in group C were 35.2% and 25.6%, respectively, while those in group D were 57.8% and 57.8%, respectively (Fig. 3). When comparing groups B and D with regard to CDDP, the survival rates for the group D patients tended to be better than those for group B.

#### Side Effect

Both the CR and HCR regimens were well tolerated, and no serious problems were observed. Although bone marrow suppression was transiently observed in some patients, almost all patients recovered by the time of operation. No severe renal dysfunction, which is known to be a major side effect of CDDP, was observed in the patients given CDDP either with or without hyperthermia. The most common side effects observed in hyper-

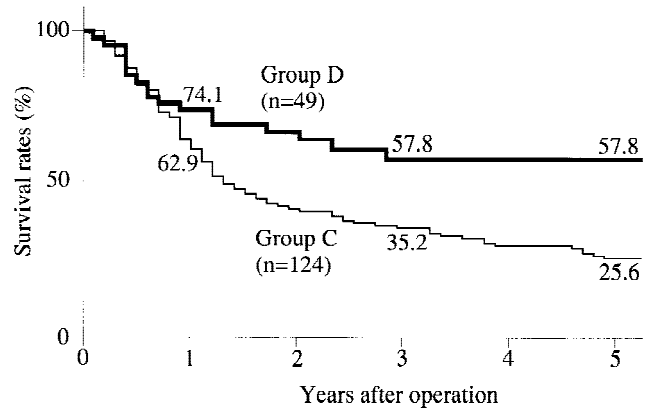


Fig. 3. The survival curves of the patients undergoing esophagectomy after HCR regarding the regimen. Statistically significant value,  $P = 0.032$ .

thermia were local heat sensation and a slightly elevated body temperature and both were easily managed.

#### DISCUSSION

The most reliable treatment for malignant disease of the esophagus is surgical removal. However, less than half of all such patients are appropriate candidates for surgery because the majority of them have widespread disease at the time of detection. Therefore, the treatment results for esophageal cancer patients still remain unsatisfactory. In our department, preoperative treatment has been aggressively applied to patients diagnosed to have advanced esophageal cancer in order to enable a complete removal of the lesion. Of the 736 cases that had been surgically treated from 1965 to March 1997 in our department, 495 cases (67.3%) had undergone some type of preoperative treatment.

In our experimental observations, hyperthermia has been shown to have an antitumor effect and to decrease the proliferation of tumor cells, while it also has a synergistic response when combined with radiotherapy and chemotherapy [12–15, 22–24]. Moreover, this treatment has the advantage of enabling us to establish the minimal doses of anticancer agents. In other words, the chief merit of combining these three modalities is an enhancement of the antitumor effects and a reduction in the side effects of each modality as a result of the diminished doses. We have already reported the long-term results and the histopathological effects of preoperative HCR. These studies suggest that preoperative HCR may be a more beneficial therapy than preoperative radiation therapy alone or radiation plus chemotherapy without hyperthermia [29–33]. The current study also clarified that the histopathological effectiveness of the HCR group was greater than that of CR group ( $P < 0.05$ ) and the survival rate of the HCR group also tended to be better than that of the CR group in the recent period. We therefore consider



preoperative HCR to be the best choice of preoperative therapy for patients with advanced esophageal cancer.

In this report, we compared the local effect and the long-term effect of preoperative CR or HCR for patients with esophageal cancer based on each regimen, respectively. As a result, it was clarified that these preoperative treatments have dramatically improved after the introduction of CDDP. Our data demonstrated the cumulative 5-year survival rate of the regimen using CDDP to be better than that of the regimen using BLM. It should be noted that both the operative techniques and the preoperative or postoperative management have improved greatly, thus resulting in higher survival rates in patients with esophageal cancer who have been surgically treated in recent years. Our data also showed that remarkable advances were recognized not only in the long-term effect but in the local effect as well. We thus conclude that these advances are due mainly to advances in our preoperative treatments. Furthermore, since recent reports [35–38] show that the combination of CDDP and 5-FU is one of the most effective chemotherapeutic regimens for the patients with esophageal cancer, this combination is now applied to both our preoperative CR and HCR regimens. Although it is too early to evaluate the long-term results of this regimen, some cases have certainly shown a markedly effective local response. A further evaluation of this regimen is called for in the future.

However, some problems regarding HCR remain to be solved. First, there are some cases that do not respond to HCR. In fact, 13 cases (26.5%) did not respond well to the therapy, although they were given regimen B. It is thought that many factors thus influence the sensitivity of preoperative treatment. We previously reported some parameters of hyperthermoradiosensitivity based on the findings of the succinate dehydrogenase inhibition (SDI) test [40] and DNA ploidy [41]. The sensitivity to CDDP is also considered to be an important factor in the effectiveness of this treatment [42–45]. If we determine the sensitivity of each case to HCR before treatment, we would be able to select cases that might respond well to HCR. Second, there is an insufficient placement of the applicator, especially for tumors that are far advanced. The narrowest intraluminal applicator, among those we used, was 10 mm in diameter. However, it is sometimes difficult for the patients with far advanced esophageal cancer to place even the narrowest applicator. We think that such patients are not indicated to undergo HCR. The development of better equipment is thus also called for.

Finally, preoperative HCR is a therapy that is followed by an operation. Therefore, the regimen of preoperative HCR should be decided prudently while carefully observing both the effectiveness and side effects of such treatment. We hope that preoperative HCR for patients with esophageal cancer will in the future play an even

more important role in the treatment of esophageal cancer patients.

## CONCLUSIONS

Preoperative HCR has improved remarkably thanks to the advances in anticancer agents and continues to show great promise for the treatment of patients with advanced esophageal cancer compared to preoperative CR. However, it is important to continue to clarify the factors influencing the effectiveness of preoperative HCR.

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